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Circadian rhythms in innate immunity and stress responses

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Summary

Circadian clocks are a common feature of life on our planet, allowing physiology and behaviour to be adapted to recurrent environmental fluctuation. There is now compelling evidence that disturbance of circadian coherence can severely undermine mental and physical health, as well as exacerbate pre-existing pathology. Common molecular design principles underpin the generation of cellular circadian rhythms across the kingdoms, and in animals, the genetic components are extremely well conserved. In mammals, the circadian timing mechanism is present in most cell types and establishes local cycles of gene expression and metabolic activity. These distributed tissue clocks are normally synchronized by a central pacemaker, the suprachiasmatic nuclei (SCN), located in the hypothalamus. Nevertheless, most clocks of the body remain responsive to non-SCN-derived hormonal and metabolic cues (for example, re-alignment of liver clocks to altered meal patterning). It has been demonstrated that the clock is an influential regulator of energy metabolism, allowing key pathways to be tuned across the 24-hr cycle as metabolic requirements fluctuate. Furthermore, clock components, including Cryptochrome and Rev-Erb proteins, have been identified as essential modulators of the innate immune system and inflammatory responses. Studies have also revealed that these proteins regulate glucocorticoid receptor function, a major drug target and crucial regulator of inflammation and metabolism.

Keywords: circadian; glucocorticoid; immunity; inflammation; innate.

Introduction

Circadian rhythms in biology have been naturally selected across all three domains of life.[1] The environmental conditions on Earth continuously change over a 24-hr period, due to the planet's axial rotation modulating exposure to the sun. Survival benefits can be gained from the ability to predict the daily changes in environment, and evolution has therefore favoured cells and organisms that employ circadian timing mechanisms.

The molecular circadian clock in cells consists of interlocking transcription–translation feedback loops, which cause regular oscillations in a set of transcription factors, known as core clock proteins.[2] Primarily these include Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-Like 1 (BMAL1; alternatively ARNTL), which form a heterodimer at E-box genomic regulatory features and drive the expression of Period (PERs) and Cryptochrome (CRYs) transcripts. PER and CRY proteins subsequently modulate their own expression by inhibiting CLOCK–BMAL heterodimers, creating an oscillation in expression. Auxiliary feedback loops exist, including RORα, which induces BMAL1 expression in a feed-forward loop and Rev-Erbs (NR1D1 and NR1D2), which repress BMAL1, competing for DNA-binding sites with RORs, in a negative feedback loop.

Abbreviations: BMAL, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; DBP, D-box binding PAR bZIP transcription factor; GC, glucocorticoid; GR, glucocorticoid receptor; HSPC, haematopoietic stem cell progenitor cell; IL-5, interleukin-5; LPS, lipopolysaccharide; NFIL3, nuclear factor, interleukin-3 regulated; PER, period; SCN, suprachiasmatic nuclei; TLR, toll-like receptor

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Additionally, D-box binding PAR bZIP transcription factor (DBP) and nuclear factor, interleukin 3 regulated (NFIL3) regulate genes, including PERs, which contain D-box motifs in their promoters. The sum of these interacting feedback loops is a robust oscillation in activating and repressing transcription factors, which cycles over approximately 24 hr.[3]

Mammals possess a master circadian pacemaker, located in the hypothalamic suprachiasmatic nuclei (SCN), which receive direct environmental light input from photoreceptors in the eye. The clock in the SCN entrains the peripheral cell clocks, which are found in nearly every cell of the body.[4] Entrainment cues generated by the SCN include oscillations in sympathetic nervous stimulation, body temperature and glucocorticoid secretion, although specific tissues may also be entrained by behavioural cues such as feeding. Internal synchrony between circadian clocks in different cell types and tissues within an organism is of fundamental importance to the maintenance of organismal health. This link between circadian rhythms and health is demonstrated by the observation that lifestyles that involve prolonged circadian disruption, such as chronic shift work, are associated with higher risk of cardiovascular disease, various cancers, cerebrovascular disease and metabolic disorders.[5] In addition, many human diseases exhibit circadian rhythmicity in their symptoms and pathology, including asthma, rheumatoid arthritis and other disorders of the immune system. Indeed, the involvement of circadian clocks in the immune system was first evidenced in 1960, when it was observed that host response to infection and endotoxins was time-of-day dependent.[6]

The innate immune system is a vertebrate host defence strategy that contrasts with, and is complimented by, the adaptive immune response. The innate immune system is normally thought of as an organism's 'first line of defence', employing various defence mechanisms against invading pathogens, including anatomical barriers, recognition of pathogens, inflammatory response and recruitment of the adaptive immune system. The adaptive immune system is a more recently evolved immunity strategy involving pathogen-specific responses based around antigen recognition and antibody production. For the purposes of this review, we will focus only on the innate immune system.

Anatomical barriers

The first and most fundamental innate defence strategy that all vertebrates employ is the construction and maintenance of anatomical barriers. Important anatomical barriers for the immune system include the skin, lungs, gut and blood–brain barrier. Each of these structures attempts to maintain impermeability to pathogens through specific mechanisms, and evidence of circadian rhythms governing these functions has been found in each. The gut serves as a particularly good example because it is colonized by many potentially pathogenic bacteria, and rhythmic barrier function is of particular importance here because of the rhythmic nature of feeding in many animals. This is evidenced by the observations that shift workers, who have disrupted circadian rhythms and disrupted feeding habits, have significantly higher rates of inflammatory bowel diseases, gastric and intestinal ulcers, and colorectal cancers.[7] Interestingly, these diseases are all associated with compromised gut barrier function resulting in increased infiltration of lipopolysaccharide (LPS), a key component of Gram-negative bacterial cell walls. Animal models have been used to study the precise mechanisms of barrier function in the gut. Chronic circadian disruption in mice was found to promote gut leakiness to pathogens in a model of alcohol-induced intestinal barrier dysfunction,[8] and these changes in inflammatory milieu and microbiota may also be directly linked to colon carcinogenesis.[9] The effects of alcohol on intestinal inflammation may be directly induced by the core circadian transcription factors, as alcohol-induced oxidative stress induced the expression of PER2 and CLOCK via cAMP response element-binding protein and the protein kinase A pathway.[10] Similarly, in a model of dextran sodium sulphate-induced colitis, disruption of core clock function either by genetic interference or environmental (light) exposure increased susceptibility to severe intestinal inflammation and epithelial dysregulation. Furthermore, a Clock Δ19 mutant was associated with intestinal dysbiosis, indicating crosstalk between the gut circadian clock and the microbial community.[11]

Taken together these observations indicate that a stable circadian rhythm in mucosal membranes is integral for effective barrier function.

Immune cells

The most important effector cells of the innate immune system are the white blood cells. The abundance of innate immune cells throughout the body is regulated by the circadian clock, through the release of haematopoietic stem progenitor cells (HSPCs) from the bone marrow into the circulation. It was in fact found that there are two daily peaks of HSPC activity, initiated by the onset of the light and the dark phases, and both are characterized by transient increases in bone marrow norepinephrine and tumour necrosis factor secretion.[12] During the onset of the light phase, tumour necrosis factor stimulates HSPC differentiation and increases vascular permeability, whereas in the dark phase, melatonin secretion is associated with renewal of HSPCs and modulation of surface CD150 and c-Kit expression to potentiate long-term repopulating stem cells.[12] HPSCs differentiate into a variety of mature innate immune cells, including monocytes, macrophages,

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neutrophils, eosinophils and natural killer cells, all of which contain their own cell-intrinsic circadian clocks.[13–18]

In the context of circadian biology, macrophages and monocytes are probably the most extensively studied cell types of the immune system to date. They exhibit robust circadian oscillations in core clock genes, as well as clock-controlled genes and physiological functions.[14,19] Macrophages perform a number of key roles within the innate immune system, and it has become increasingly clear that macrophage function is extremely context-specific. It is of particular importance to note the distinction between monocyte-derived macrophages and tissue-resident macrophages. Whereas monocyte-derived macrophages are derived from haematopoiesis and recruited to tissues during inflammation, tissue-resident macrophages are a heterogeneous population of cells that are self-renewing and their phenotype is controlled largely by the tissue environment.[20]

Tissue-resident macrophages are thought to play a key role in the detection of invading pathogens in many tissues. This is predominantly mediated by toll-like receptor (TLR) expression. A recent study in murine splenic macrophages determined that all TLRs (TLR1–8), with the sole exception of TLR5, are expressed rhythmically.[21] Once a pathogen is detected, an important innate role of macrophages is phagocytosis. Phagocytic and bactericidal activity was demonstrated to be dependent on circadian phase and coincided with different states of mitochondrial dynamics – specifically mitochondrial fusion and high membrane potential.[22] Intriguingly, cytokine production in macrophages is stimulated by phagocytosis, but the rhythms in cytokine production and phagocytosis efficiency appear to be independent of one another when examined in *ex vivo* peritoneal macrophages as well as *in vivo*.[23] These studies all indicate that circadian mechanisms tune macrophages to optimize host defence against bacteria at specific times of day. Furthermore, control of innate defence mechanisms against viral pathogens (including herpes virus and influenza virus) and eukaryotic parasite pathogens (*Leishmania*) has also been demonstrated to be under circadian control.[24–26] Intriguingly, although clearance of the fungal pathogen *Aspergillus fumigatus* from the lungs of mice was found to be under circadian control, the phagocytic activity of macrophages in *ex vivo* culture did not vary over time. This may indicate that cell types other than the macrophage are important for innate circadian timing of defence against fungal insult.[27]

Another key function of tissue-resident macrophages is cytokine secretion. Time-of-day gating of macrophage cytokine release in response to canonical innate stimuli, such as the TLR4 agonist LPS, has been shown in both mouse and human macrophages *in vitro*.[14,19] The TLR4-mediated physiological response to LPS is also regulated in a circadian manner. Indeed, mice challenged with LPS *in vivo* at CT12 were twice as responsive to systemic (intraperitoneal) LPS administration as those challenged at CT0. This response was further shown to be dependent on a competent macrophage intrinsic cell clock.[19]

Stimulated macrophages secrete cytokines to recruit other innate defence cell types to sites of infection, including neutrophils and natural killer T cells. Neutrophils are the most abundant mammalian granulocyte and are rapidly recruited to sites of infection by chemotaxis. Circadian variation in neutrophil functions including phagocytosis, superoxide production and expression of adhesion molecules has been reported.[17,28–30] Core clock gene expression in neutrophils, however, is less dynamic and generally lower compared with other leucocytes.[17] This has raised the question as to whether rhythmic neutrophil responses are controlled by an intrinsic molecular clock or by external circadian stimuli.[31] Indeed, *Per1* expression in neutrophils was found to be sensitive to cortisol *in vitro* and followed circadian changes in plasma cortisol *in vivo*. Neutrophils are relatively short-lived compared with other leucocytes, and this may result in a reduced requirement for an intrinsic cell clock. However, neutrophil recruitment is strongly rhythmic in models of inflammation, because of circadian variation in the strength of recruitment signals from other cell types.[26,32–34] Other studies have implicated the sympathetic nervous system, acting through β-adrenoreceptors to cause rhythmic expression of pro-migratory factors intercellular adhesion molecule 1 and CCL2 in endothelial cells.[35] Furthermore, clearance of aged neutrophils towards the end of the daily rest phase in mice is regulated by bone-marrow-resident macrophages.[36] Similarly, feeding-induced hormonal cues influence interleukin-5 (IL-5) and IL-13 cytokine production by a subset of group-2 innate lymphoid cells, thereby influencing circadian recruitment of blood eosinophils to peripheral tissues.[37]

To understand the mechanisms by which circadian clocks modulate innate immunity, work has been focused on studying the effect of circadian disruption in models of inflammation. Much of this work has been done using murine models where core clock components have been genetically disrupted, either globally or in targeted innate cell types such as macrophages. It is important to note here that disruption of *Bmal1* in a cell will effectively stop the clock ticking, whereas disruption of other core clock components alone will not necessarily stop the clock, but may modulate parameters of the oscillations such as period and amplitude.[38]

The circadian clock was shown to be directly responsible for rhythms in systemic TLR4-mediated inflammation as macrophage-specific deletion of *Bmal1* abrogated the time-of-day effect.[19] Disruption of *Bmal1* in macrophages completely disabled the clock in this cell type, demonstrating that macrophages are responsible for the time-of-day responsiveness to systemic TLR4-mediated inflammation. It was further shown that macrophage-specific deletion of *Rev-Erbα* was also sufficient to disrupt the circadian

regulation of the systemic inflammatory response, despite the fact that in this instance the macrophages remain rhythmic in this model. This observation makes Rev-Erbα a prime candidate for linking the macrophage clock to inflammatory processes.[19] A study looking at *Bmal1* disruption in monocytes found that circadian oscillations in monocyte numbers in blood, spleen and bone marrow were dependent on a functional cell clock.[39] Furthermore, animals with *Bmal1*-deficient monocytes were more susceptible to a non-lethal dose of *Listeria monocytogenes*, which acts through TLR2 and TLR5,[40,41] exhibiting reduced median survival times and higher circulating pro-inflammatory cytokine concentrations.[39] Mechanistic studies in this model revealed that *Bmal1* can recruit polysome repressive complex 2 complex to repress the expression of chemokine genes, including *Ccl2* and *Ccl8*.[39] Other mechanistic studies of BMAL1 function have identified direct binding to E-box sites in the promoter region of *Nrf2*. Deletion of *Bmal1* in macrophages decreased the *Nrf2* induction after LPS stimulation, leading to a reduced glutathione synthesis, a curtailed antioxidant response as well as ROS accumulation and increased production of IL-1β.[42] Other studies of BMAL1 function in macrophages have implicated the involvement of miR-155, which is expressed rhythmically and can repress BMAL1 function directly.[43]

Macrophages in other tissues have also been shown to be important regulators of the circadian innate immune response. BMAL expression was important for IL-6 upregulation in microglia in response to LPS and in a murine model of stroke.[44] Splenic natural killer cells were dependent on PER1 expression to modulate rhythmic expression of interferon-γ, perforin and granzyme B.[45]

These observations indicate that different cell types may orchestrate the circadian innate immune response in different tissues. A particularly striking example of this is the observation that mice lacking *Bmal1* in the macrophage still exhibit rhythmic responses to aerosolized LPS, as measured by neutrophil recruitment and cytokine production in the lung.[32] This indicates that the macrophage clock is dispensable for time-of-day gating of the inflammatory response in the lung, which is in contrast to systemic LPS exposure. As it turns out, it is in fact the epithelial cell clock that is responsible for regulating time-of-day gating of the inflammatory response in the lung, as demonstrated using clara cell secretory protein-icre to drive specific *Bmal1* deletion in a subset of lung epithelial cells.[32] Together, these observations highlight that in different tissues, and in response to different stimuli, there may be different hierarchies of peripheral cell clocks.

Inflammation remodelling the clock

Inflammation plays a critical role in many human diseases, and safe effective treatments remain an unmet and urgent clinical need. Consistent findings in chronic inflammation are attendant insulin resistance and accelerated cardiovascular disease, with evidence suggesting a causal role of aberrant energy metabolism. The circadian clock exerts regulatory control over immune processes through finely tuned molecular mechanisms, for example, the powerful circadian constraints on innate immune responses via the clock proteins BMAL1 and Rev-ErbA. Critically, this coupling between the circadian clock and inflammation is reciprocal (Fig. 1), wherein the circadian clock is subject to inflammation-mediated reprogramming, with eventual disruption of the clock mechanism.[46]

Immune and inflammatory responses come at a high energetic cost and therefore necessitate that immune and metabolic processes are coupled to ensure energetic demands are met. We propose that the circadian clock is such a coupling mechanism, and that during inflammation the circadian processes are extensively re-organized, with attenuation of many usual transcriptional rhythms and *de novo* genesis of surrogate cycling pathways. For example, it has been recently demonstrated that degradation of Rev-ErbA, a core cellular clock protein and nuclear hormone receptor, is greatly accelerated by active inflammation,[34] and that loss of this component of the clock shifts the nature of the immune response.[19] Similar effects of inflammation on Rev-ErbA have been reported in colitis, with again a reciprocal relationship between the clock and inflammation.[47] This reprogramming of circadian processes is a likely requirement in immune cells and local sites of inflammation; however, there is evidence of a progression to widespread clock disruption (e.g. in liver) that then drives systemic metabolic disorders. Indeed, Rev-ErbA-mediated regulation of lipid metabolism is well established, and global deletion of this factor leads to dyslipidaemia, hepatosteatosis and obesity.[48]

Stress responses

One of the key endogenous regulators of inflammation is the glucocorticoid (GC) cortisol in humans (corticosterone in rodents). Secretion of cortisol in humans (or corticosterone in rodents) from the adrenal glands follows a strong circadian pattern, peaking in the serum before the active phase (daytime in humans, night time in rodents).[49] GCs work by activating the glucocorticoid receptor (GR) transcription factor, causing nuclear translocation leading to transactivation and transrepression of GR target genes.[49] Synthetic GCs are the most potent anti-inflammatory therapy available and are widely used in a variety of disease pathologies, however, frequent therapeutic use leads to severe side effects including fat accumulation, hyperglycaemia and hepatosteatosis.[50] Many of these side effects are shared with the deleterious outcomes of prolonged circadian disruption. Indeed, a number of studies have begun to elucidate the intricate crosstalk between GCs and the circadian clock.

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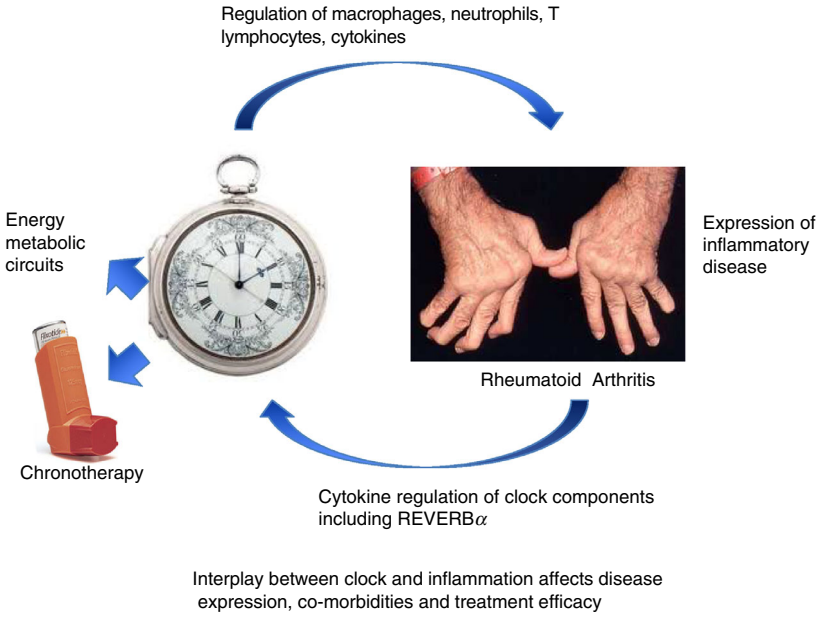

Figure 1. Interplay between the circadian clock and inflammation. The circadian cell clock operates in multiple cell types of the innate immune system, including macrophages, neutrophils and lymphocytes. The innate immune functions of these cells are gated by time of day, leading to circadian exacerbations of inflammatory diseases, such as rheumatoid arthritis. Furthermore, inflammatory mediators, such as cytokines, feedback to regulate the expression of components of the circadian clock. Chronotherapy may represent an important strategy to increase the efficacy of new and existing anti-inflammatory drugs, as well as reducing the impact of undesired side effects.

Endogenous GC release is under the control of the circadian clock; however, GCs themselves are known to be potent re-setters of the circadian clock.[51] GC secretion *in vivo* is important for circadian time-keeping of peripheral clocks as adrenalectomized mice are able to adjust phase more quickly.[52,53] When endogenous GC rhythms were abolished in mice by adrenalectomy, rhythmic pulmonary inflammatory responses to aerosolized LPS were also lost along with the circadian regulation of CXCL5 production.[32] Furthermore, GR occupancy at the Cxcl5 locus is circadian, but disrupted in Bmal1-deficient lung epithelial cells. This suggests a key role for the adrenal axis in circadian control of innate inflammatory responses. Reciprocally, the anti-inflammatory effects of dexamethasone, including reduced neutrophilia and CXCL5 production after aerosolized LPS, were dependent on an intact cell clock in airway epithelial cells. In a separate study, a corticosterone clamp was used to eliminate rhythmic secretion of endogenous GCs by feedback repression while maintaining the availability of GR ligand. Under these conditions, rhythmic innate inflammatory responses, including neutrophilia and CXCL5 production, persisted.[33] This suggests that it is circadian rhythms in GR function rather than ligand availability that are important for regulating immune function. Indeed, transcriptome profiling of whole lung after exposure to the synthetic GC dexamethasone revealed that 57% of GC-regulated genes are time-of-day dependent.[54] Direct interactions at the level of the genome between GR and core clock genes including Cryptochromes and Rev-Erbs have been demonstrated and may underlie these observations.[54,55] Intriguingly, although genetic ablation of GR in airway epithelial cells abolished rhythmic CXCL5 production it did not affect circadian gating of LPS-mediated neutrophil recruitment. This indicated additional clock-controlled factors operating to gate neutrophil recruitment to the lung, which were shown to be dependent on macrophage GR expression.[33] Further evidence of a functional link between stress responses and the circadian clock includes a recent study showing that the stress response, as measured in rodents by circulating corticosterone level after restraint, is exaggerated by high-fat diet only at specific times of day.[56]

Therapeutic implications

Fifty years ago, it was recognized that regulation of cholesterol synthesis in the liver was highly circadian and, indeed, that short-acting drugs that inhibit the biosynthetic pathway only work in humans when given at night. It might have been the dawn of a new era in chronomedicine, but despite trial evidence for differential efficacy with inhaled GCs in asthma,[57–59] there has been very little development of timing as a factor in drug development, drug trial design or practical administration.

The interdependence of timing and effect has perhaps been most studied in chronic inflammation, many of the diseases driven by unresolving inflammation show strong

circadian variation. For example, chrono-modified GCs have been used in the clinic to treat rheumatoid arthritis.[60] In fact, the time of day, and circadian clock in target organs play a major role in modifying the action of GC drugs, though interactions with the cryptochrome system,[61] and the Rev-Erb proteins.[54]

Close cross-coupling between the cellular circadian clock and the GR is supported by overlapping roles in regulating energy metabolism and immunity. In terms of energy metabolism, cryptochromes impact GC regulation of liver GR carbohydrate metabolism, and the physical interaction, and functional cooperativity between GR and Rev-ErbA, seem to mainly affect liver lipid metabolism.[54] It may be that timed administration of glucocorticoids can be a powerful tool in targeting specific physiological programmes, for example by avoiding the detrimental metabolic actions of GCs in the liver while maintaining anti-inflammatory activity.

Summary

The circadian clock has emerged as a major regulator of innate immunity, with effects manifest in professional immune cells, including macrophages, as well as stromal cells, such as the airway epithelium. In turn, inflammation feeds into the clock, mainly acting on the expression, stability and function of the Rev-Erb clock components. There is disruption of the circadian clock control of bioenergetics pathways in response to inflammation, and surprisingly some biochemical pathways only acquire circadian regulation when under inflammatory stress.

The interdependence seen between the core clock and inflammation has major implications for therapy, with some commonly used anti-inflammatory drugs showing time-of-day variation in therapeutic response, and also off-target toxicity.

Disclosures

The authors declare that there are no competing interests.

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